Remarks

Claims 37, 40, 41, 44 and 45 were examined in the Office Action dated February 5, 2002 and rejected based on 35 USC §103(a). This rejection is believed to be overcome in part by the above amendments and is otherwise traversed for reasons to be discussed below. Applicants note with appreciation the withdrawal of the previous obviousness-type double patenting rejection.

Overview of the Above Amendments:

Claim 37 has been amended to recite the invention with greater particularity. Specifically, minor wording changes have been made to the claims to clarify the relationship of the antigen and carrier protein. Support for these amendments can be found in the previous claims as well as throughout the specification. Accordingly, no new matter has been added to the application by way of these amendments.

A copy of the elected claims, incorporating the amendments made herein, is provided for the Examiner's convenience.

Rejection Under 35 USC §103:

Claims 37, 40, 41 and 45 were rejected under 35 USC §103(a), as being unpatentable over U.S. Patent No. 5,476,657 to Potter ("Potter") in view of U.S. Patent No. 5,114,711 to Bell et al. ("Bell"). The Examiner argues that Potter discloses linking a Pasteurella protein to a carrier to increase the immunogenicity of the protein. The Office correctly acknowledges that Potter fails to show chimeric proteins comprising a *P. haemolytica* leukotoxin and a peptide hormone. Bell is cited for teaching the recombinant production of chimeric proteins with two covalently linked cell modulators in a linear polypeptide sequence. The Examiner argues that Bell defines cell modulators as including peptide hormones. The Examiner contends:

> It would have been obvious to one of ordinary skill in the art at the time the invention was made that a peptide hormone as disclosed by Bell et al. could be linked to at least one epitope of a leukotoxin derived from P. haemolytica, as taught by Potter, because the leukotoxin is a cytotoxin which Bell specifically teaches may be linked to peptide hormones, for a dual immune modulating effect. One of ordinary skill in the art would expect to increase the immune response to the leukotoxin and produce a more efficient vaccine against respiratory disease in ruminants by linking to an immune modulator.

Office Action, pages 4-5, bridging paragraph. However, applicants submit that the Action has failed to establish a *prima facie* showing of obviousness.

In particular, the inventive concept underlying the present application is that the immunogenicity of a peptide hormone (an antigen) can be boosted by presenting it to the immune system coupled with a leukotoxin polypeptide (a novel carrier).

Bell refers to chimeras of polypeptide cell modulators, "each of which acts through a different and specific cell receptor to initiate complementary biological activities" (col. 1, lines 12-15). As recognized by the Examiner, polypeptide cell modulators are generally defined as including lymphokines, monokines, interferons, cytotoxins, peptide hormones and peptide growth factors (col. 1, lines 15-18 and col. 3, lines 60-64), i.e. an enormous range and variety of different molecules with diverse functions. In the class of cytokines alone, more than 50 different polypeptides are mentioned (col. 4, lines 4-28). Leukotoxins are never specifically mentioned as examples of cytotoxins.

In view of the very broad and superficial disclosure of Bell, applicants dispute the Examiner's assertion that Bell et al. "specifically disclose that cytotoxins and peptide hormones may be linked together to treat disease" (page 4 of the Office Action). Nowhere in Bell is it suggested to specifically select cytotoxins and peptide hormones to be juxtaposed in a chimera. Bell merely describes a chimera comprising a human lymphotoxin (cytotoxin) and a human gamma interferon. Interferons and

peptide hormones are distinct entities (see, e.g., col. 1, lines 15-18 and col. 3, lines 60-64).

Potter discloses that the immunogenicity of Pasteurella antigens (including leukotoxins) in a vaccine against pneumonia may be improved by linkage to a carrier (col. 13, lines 9-50). The list of conventional carriers includes proteins such as serum albumin, keyhole limper hemocyanin, immunoglobulin molecules, thyroglobulin, ovalbumin, rotavirus VP6 polypeptides, or other proteins known to those skilled in the art (col. 13, lines 13-49). Crucially, Potter does not disclose that a leukotoxin could *itself* perform as a carrier (note the definition of a "carrier system" in the present application). As is pointed out on the first page of the application, carriers may elicit strong immunity not relevant to the peptide antigen and this may actually inhibit the immune response to a peptide vaccine. Thus, the skilled person armed with the knowledge from Potter that leukotoxin can be used as a vaccine antigen would not make any assumptions about the practicality of using leukotoxin as carrier, and especially as a carrier for peptide hormones.

The Examiner's position is that one skilled in the art would try to improve the immunogenicity of Potter's leukotoxin antigens in order to produce a more efficient vaccine against respiratory disease in ruminants by linking to an immune modulator of a type recited in Bell (such as peptide hormone). But Bell is completely silent on the immunogenicity of the chimeras and is not concerned with creating a vaccine. Therefore, Bell is irrelevant to the field of vaccine development. Furthermore, there is no guidance in Bell regarding which of the vast number of different polypeptide cell modulators might be suitable for linking to a leukotoxin antigen. For the sake of argument, if a skilled person were nevertheless to contemplate constructing a leukotoxin-peptide hormone chimera, Bell teaches only that one might hope to obtain

complementary leukotoxin activity and peptide hormone activity (but not immune modulating activity).

The claims have been amended in order to emphasize that this situation is reversed in the present invention. To reiterate, it is the peptide hormone which is the antigen to which an improved immune response is sought. Bell would not have been consulted by the skilled person because it is not concerned with finding compatible antigen-carrier combinations for vaccines. A skilled person seeking to improve the immunogenicity of a peptide hormone could have chosen a conventional protein or non-protein carrier, such as those referred to in Potter. However, applicants assert that under no circumstances would the skilled artisan have arrived at the solution described in the present application, because he could not have known that a leukotoxin as defined in the claims would be effective as a carrier in stimulating an immune response to the peptide hormone.

On the other hand, the applicants herein have convincingly demonstrated that the combination of antigen and carrier as defined in the amended claims provides a highly-immunogenic chimeric molecule capable of being used as an effective vaccine.

Based on the foregoing, applicants submit that the Action has failed to establish a *prima facie* showing of obviousness. Reconsideration and withdrawal of the rejection of the claims under 35 USC §103 is therefore respectfully requested.

Conclusion

Applicants respectfully submit that the claims comply with the requirements of 35 USC §112, and define an invention which is novel and nonobvious over the art. Accordingly, allowance is believed to be in order, and an early notification to that effect would be appreciated.

If the Examiner notes any further matters which she believes may be expedited by a telephone interview, she is requested to contact the undersigned attorney at (650) 325-7812.

Respectfully submitted,

By: _____
Roberta L. Robins
Registration No. 33,208

ROBINS & PASTERNAK LLP
545 Middlefield Road, Suite 180
Menlo Park, CA 94025
Telephone: (650) 325-7812
Fax: (650) 325-7823

Version with markings to show changes made

In the Claims:

Claim 37 has been amended as follows:

37. (Twice amended) A chimeric protein comprising an antigen coupled to a carrier protein, wherein said carrier protein is a leukotoxin polypeptide that activates helper T-cells[, coupled to] and said antigen is a selected peptide hormone which is not a cytokine, and further wherein said leukotoxin polypeptide is an RTX leukotoxin from a bacterium selected from the group consisting of *Pasteurella haemolytica*, *E. coli* and *Actinobacillus pleuropneumoniae*.

Currently Pending Claims

37. (Twice amended) A chimeric protein comprising an antigen coupled to a carrier protein, wherein said carrier protein is a leukotoxin polypeptide that activates helper T-cells and said antigen is a selected peptide hormone which is not a cytokine, and further wherein said leukotoxin polypeptide is an RTX leukotoxin from a bacterium selected from the group consisting of *Pasteurella haemolytica*, *E. coli* and *Actinobacillus pleuropneumoniae*.

40. The chimeric protein of claim 37, wherein said leukotoxin polypeptide is coupled to gonadotropin releasing hormone (GnRH), or an epitope thereof.

41. The chimeric protein of claim 40, comprising the amino acid sequence of SEQ ID NO:12.

44. The chimeric protein of claim 37, wherein the leukotoxin polypeptide is a *Pasteurella haemolytica* leukotoxin polypeptide.

45. The chimeric protein of claim 40, wherein the leukotoxin polypeptide is a *Pasteurella haemolytica* leukotoxin polypeptide.